Molecular Crystals and Liquid Crystals

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl20

Crystal Structure of Lamotriginium Hydrogen Phthalate Dimethylformamide Solvate (1:1:1)

Balasubramanian Sridhar [a] & Krishnan Ravikumar [a]

[a] Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad, India

Version of record first published: 31 Jan 2007

To cite this article: Balasubramanian Sridhar & Krishnan Ravikumar (2006): Crystal Structure of Lamotriginium Hydrogen Phthalate Dimethylformamide Solvate (1:1:1), Molecular Crystals and Liquid Crystals, 461:1, 131-141

To link to this article: http://dx.doi.org/10.1080/15421400600983556

Mol. Cryst. Liq. Cryst., Vol. 461, pp. 131–141, 2007

ISSN: 1542-1406 print/1563-5287 online
DOI: 10.1080/15421400600983556

Taylor & Francis
Taylor & Francis Group

Crystal Structure of Lamotriginium Hydrogen Phthalate Dimethylformamide Solvate (1:1:1)

Balasubramanian Sridhar and Krishnan Ravikumar
Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad, India

The title compound, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine-hydrogen phthalate-dimethylformamide, $C_9H_8N_5Cl_2^+ . C_8H_5O_4^- . C_3H_7NO$ (lamophthalate), crystallizes in the triclinic space group P1 with unit cell parameters $a = 10.1587(6)$ Å, $b = 11.3704(7)$ Å, $c = 12.1976(7)$ Å, $\alpha = 110.797(1)^\circ$, $\beta = 111.61(1)^\circ$, $\gamma = 99.53(1)^\circ$, $V = 1151.16(12)$ Å^3, and $Z = 2$. The asymmetric unit comprises one lamotriginium cation, one hydrogen phthalate anion, and one dimethylformamide solvate. The dihedral angle between the two planar rings is 65.3(1)°. The expected proton transfer occurs at N2 of the triazine ring. Both O-H…O and N-H…O hydrogen bonding stabilizes the crystal structure.

Keywords: anticonvulsant; hydrogen bonding; lamictal; protonation; triazine ring

INTRODUCTION

Lamotrigine (marketed as Lamictal by GlaxoSmithKline) is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. For epilepsy it is used to treat partial seizures, primary and secondary tonic–clonic seizures, and seizures associated with Lennox–Gastaut syndrome. Lamotrigine also acts as a mood stabilizer. It is the only anticonvulsant mood stabilizer that treats the depressive as well as the manic phases of bipolar disorders, and it is the first medication since lithium to be granted FDA approval for the maintenance treatment of bipolar I disorder. Chemically unrelated to other anticonvulsants, lamotrigine has relatively few side effects and does not require blood monitoring. It is a Na^+ channel blocker and is inactivated by hepatic glucuronidation. Lamotrigine is thought to act

Address correspondence to B. Sridhar, Room No. 150, Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology (IICT), Hyderabad 500 007, India. E-mail: sshiya@yahoo.com

at voltage-sensitive sodium channels to stabilize neuronal membranes and inhibit the release of excitatory amino acid neurotransmitters (*e.g.*, glutamate, aspartate) that are thought to play a role in the generation and spread of epileptic seizures. The most common side effects of lamotrigine are headache, nausea and vomiting, dizziness, diplpia, and ataxia [1]. Phthalic acid is a small carboxylic acid that has special relevance to environmental chemists and geochemists. It represents common functional groups found in natural organic matter [2].

Our particular interest lies in the crystalline complex of drug molecules with aromatic acids, providing a means both for a structural study of important drug and for examining the interactions among the components. In this context, we recently reported the crystal structure of lamotriginium benzoate dimethylformamide solvate [3]. In the present study, the crystal structure determination of lamotrigine with phthalic acid and dimethylformamide was undertaken, and the results are presented here.

EXPERIMENTAL

Crystal Growth

Lamotrigine and phthalic acid was mixed in a 1:1 stoichiometric ratio and dissolved in aqueous dimethylformamide solvent. Crystals were obtained by slow evaporation.

Structure Determination

X-ray data for the title compound were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å) with ω-scan method [4]. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined from the setting angles of 6413 reflections in the range of $2.25 < \theta < 27.78^{\circ}$.

Integration and scaling of intensity data were accomplished using the SAINT program [4]. The structure was solved by direct methods using SHELXS97 [5], and refinement was carried out by full-matrix least-squares technique using SHELXL97 [5]. Anisotropic displacement parameters were included for all nonhydrogen atoms. The hydrogen atoms attached to nitrogen (N2) and oxygen (O3) atoms were located in a difference density map and refined freely. All other hydrogen atoms were positioned geometrically and treated as riding atoms, with N–H $= 0.86$ Å and C–H distances in the range of 0.93–0.96 Å and with U_{iso}(H) values of $1.5U_{eq}$(C) for methyl hydrogen and $1.2U_{eq}$(C,N) for other hydrogen

atoms. The crystal and refinement data are given in Table 1. Molecular graphics were computed using the SHELXTL program [6]. The schematic diagram of the title compound is shown in Fig. 1. The perspective view of the molecules using ORTEP is shown in Fig. 2. Bond lengths, bond angles and torsion angles are shown in Tables 2, 3, and 4. Hydrogen bonding geometry is listed in Table 5.

RESULT AND DISCUSSION

The asymmetric unit of the title compound consists of a protonated moiety at one of the three nitrogen atoms of the lamotriginium cation,

TABLE 1 Crystal Data and Structure Refinement for Lamophthalate

Parameter	Value
CCDC no.	604699
Empirical formula	$C_9H_8N_5Cl_2^+.C_8H_5O_4^-.C_3H_7NO$
Formula weight	495.32
Temperature	273(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P_1
Unit cell dimensions	a = 10.1587(6) Å b = 11.3704(7) Å c = 12.1976(7) Å $\alpha = 110.797(1)^\circ$ $\beta = 111.611(1)^\circ$ $\gamma = 99.531(1)^\circ$
Volume	1151.16(12) $Å^3$
Z	2
Calculated density	1.429 Mg/m^3
Absorption coefficient	0.326 mm^{-1}
F(000)	512
Crystal size	0.21 × 0.19 × 0.09 mm
Theta range	2.02 to 25.00°
Index ranges	$-12 \le h \le 12$ $-13 \le k \le 13$ $-14 \le l \le 14$
Reflections collected/unique	11098 /4034 [R(int) = 0.0178]
Completeness	99.70%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4034/0/308
Observed reflections [I > 2σ(I)]	3559
Goodness of fit on F2	1.062
Final R indices [I > 2σ(I)]	R1 = 0.0404, wR2 = 0.1127
R indices (all data)	R1 = 0.0446, wR2 = 0.1154
Largest diff. peak and hole	0.346 and −0.278e.$Å^{-3}$

TABLE 2 Bond Lengths (Å) for Lamophthalate

Atoms	Length
C1–N5	1.322(2)
C1–N1	1.330(2)
C1–N2	1.344(2)
C2–N4	1.308(2)
C2–N1	1.331(2)
C2–C3	1.459(2)
C3–N3	1.288(2)
C3–C4	1.486(2)
C4–C5	1.390(3)
C4–C9	1.395(3)
C5–C6	1.389(3)
C5–Cl1	1.7201(19)
C6–C7	1.375(3)
C6–Cl2	1.727(2)
C7–C8	1.370(3)
C8–C9	1.378(3)
N2–N3	1.350(2)
C10–O1	1.230(2)
C10–O2	1.268(2)
C10–C11	1.517(3)
C11–C12	1.393(3)
C11–C16	1.416(2)
C12–C13	1.369(3)
C13–C14	1.372(3)
C14–C15	1.374(3)
C15–C16	1.393(3)
C16–C17	1.514(3)
C17–O4	1.218(2)
C17–O3	1.286(2)
C18–O5	1.221(3)
C18–N6	1.317(3)
C19–N6	1.443(3)
C20–N6	1.455(3)

one hydrogen phthalate anion dissociated at one of the carboxyl groups, and one dimethylformamide solvent molecule.

The hydrogen phthalate anion is almost planar and the two-carboxyl groups (dissociated and nondissociated) are coplanar (dihedral angle 3.9(2)° for both the groups) with its attached parent benzene ring. The bond length (C11–C10 = 1.517(3) Å) of the ionized carboxyl group is slightly longer than the nondissociated carboxyl group (C16–C17 = 1.514(3) Å), which is comparable with the observed value (1.491(8) Å) for the unconjugated $C_{aromatic}$ –C sp^2 bond [7].

TABLE 3 Angles (°) for Lamophthatate

Atoms	Angle
N5–C1–N1	120.49(16)
N5–C1–N2	117.66(16)
N1–C1–N2	121.85(16)
N4–C2–N1	119.45(16)
N4–C2–C3	120.60(16)
N1–C2–C3	119.95(15)
N3–C3–C2	120.52(16)
N3–C3–C4	115.66(15)
C2–C3–C4	123.81(15)
C5–C4–C9	119.46(17)
C5–C4–C3	121.27(16)
C9–C4–C3	119.16(16)
C6–C5–C4	119.80(18)
C6–C5–Cl1	120.17(15)
C4–C5–Cl1	120.01(14)
C7–C6–C5	119.95(19)
C7–C6–Cl2	119.45(15)
C5–C6–Cl2	120.60(16)
C8–C7–C6	120.45(19)
C7–C8–C9	120.5(2)
C8–C9–C4	119.77(19)
C1–N1–C2	117.06(15)
C1–N2–N3	122.87(15)
C3–N3–N2	117.11(15)
O1–C10–O2	121.51(18)
O1–C10–C11	117.68(17)
O2–C10–C11	120.80(16)
C12–C11–C16	117.56(17)
C12–C11–C10	113.86(16)
C16–C11–C10	128.56(16)
C13–C12–C11	123.3(2)
C12–C13–C14	118.94(19)
C13–C14–C15	119.61(19)
C14–C15–C16	122.58(19)
C15–C16–C11	117.97(16)
C15–C16–C17	113.58(16)
C11–C16–C17	128.44(16)
O4–C17–O3	119.38(18)
O4–C17–C16	119.75(17)
O3–C17–C16	120.86(16)
O5–C18–N6	125.4(2)
C18–N6–C19	121.2(2)
C19–N6–C20	117.6(2)

TABLE 4 Torsion Angle (°) for Lamophthalate

Atoms	Angle
N4–C2–C3–N3	171.34(18)
N1–C2–C3–N3	–7.7(3)
N4–C2–C3–C4	–7.5(3)
N1–C2–C3–C4	173.40(17)
N3–C3–C4–C5	112.72(19)
C2–C3–C4–C5	–68.3(2)
N3–C3–C4–C9	–63.4(2)
C2–C3–C4–C9	115.5(2)
C9–C4–C5–C6	1.4(3)
C3–C4–C5–C6	–174.72(16)
C9–C4–C5–Cl1	179.95(14)
C3–C4–C5–Cl1	3.8(2)
C4–C5–C6–C7	–1.2(3)
Cl1–C5–C6–C7	–179.75(16)
C4–C5–C6–Cl2	178.46(14)
Cl1–C5–C6–Cl2	–0.1(2)
C5–C6–C7–C8	0.0(3)
Cl2–C6–C7–C8	–179.72(18)
C6–C7–C8–C9	1.1(4)
C7–C8–C9–C4	–0.9(3)
C5–C4–C9–C8	–0.4(3)
C3–C4–C9–C8	175.84(17)
N5–C1–N1–C2	–178.92(18)
N2–C1–N1–C2	1.3(3)
N4–C2–N1–C1	–173.40(19)
C3–C2–N1–C1	5.7(3)
N5–C1–N2–N3	173.09(17)
N1–C1–N2–N3	–7.2(3)
C2–C3–N3–N2	2.2(3)
C4–C3–N3–N2	–178.85(15)
C1–N2–N3–C3	5.0(3)
O1–C10–C11–C12	–3.3(3)
O2–C10–C11–C12	175.78(19)
O1–C10–C11–C16	178.4(2)
O2–C10–C11–C16	–2.5(3)
C16–C11–C12–C13	0.2(3)
C10–C11–C12–C13	–178.2(2)
C11–C12–C13–C14	–0.1(4)
C12–C13–C14–C15	–0.3(4)
C13–C14–C15–C16	0.6(3)
C14–C15–C16–C11	–0.5(3)
C14–C15–C16–C17	178.95(19)
C12–C11–C16–C15	0.1(3)
C10–C11–C16–C15	178.26(18)
C12–C11–C16–C17	–179.25(18)

(*Continued*)

TABLE 4 Continued

Atoms	Angle
C10–C11–C16–C17	–1.1(3)
C15–C16–C17–O4	3.3(3)
C11–C16–C17–O4	–177.3(2)
C15–C16–C17–O3	–175.75(19)
C11–C16–C17–O3	3.6(3)
O5–C18–N6–C19	–1.2(3)
O5–C18–N6–C20	177.6(3)
O5–C18–N6–C19	–1.2(3)
O5–C18–N6–C20	177.6(3)

The molecular geometry in terms of bond lengths and angles are in a good agreement with the related lamotrigine structures *viz*. lamotrigine isoethionate [7] and lamotriginium benzoate dimethylformamide [2]. Both the triazine ring and the dichloro-phenyl ring are planar, and the dihedral angle between these rings is 65.3(1)°. The corresponding dihedral angles are 89.6(1)° and 66.08°, respectively, for lamotriginium benzoate dimethylformamide and lamotrigine isethionate. An rms overlay of dichloro-phenyl ring of the title compound, along with the other lamotriginium salts, clearly reveals the tilt of the triazine ring (Fig. 3.). In general, the dihedral angle is observed in the range of 50–80° in the reported lamotrigine structures [8–13]. The presence of substituents at the ortho positions with respect to the central C–C bond may attribute for the relatively large values. In the absence of such a hindrance, the twist is much smaller (dihedral angle 9.3(1)°) as observed in the crystal structure of 5-(p-chlorophenyl)-1,2,4-triazine [14].

The N–N (1.350(2) Å) and the four C–N (mean value 1.323(2) Å) bond distances of the triazine ring are intermediate between the expected single (1.45 and 1.47 Å) and double (1.20 and 1.27 Å) bond distances. The side group C–N (mean value 1.333(2) Å) bond distance

TABLE 5 Hydrogen Bonding Geometry (Å and °) for Lamophthalate

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N2-H2N...O1	0.83(2)	1.85(2)	2.676(2)	172(2)
N4-H4A...O5#1	0.86	2.03	2.861(2)	162.2
N4-H4B...O5#2	0.86	2.04	2.853(2)	156.3
N5-H5A...O4#3	0.86	2.08	2.920(2)	165.3
N5-H5B...O2	0.86	2.1	2.957(2)	172.3
O3-H3O...O2	0.88(3)	1.53(3)	2.404(2)	176(3)

Note: 1) x + 1, − y + 1, − z + 1; 2) x + 1, y, z + 1; 3) − x, − y + 1, − z + 1.

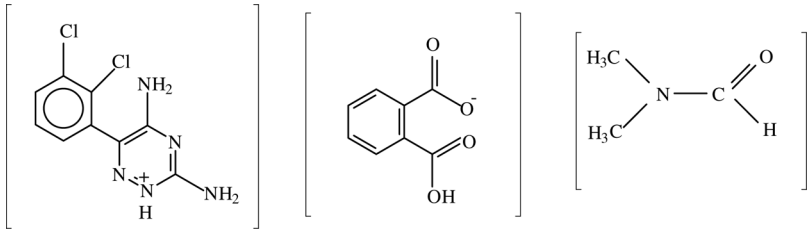

FIGURE 1 Schematic diagram of the title compound.

is well comparable with the reported mean value of 1.330(10) Å. In the triazine ring, the bond angle C1–N2–N3, 122.9(2)°, is comparatively long, whereas the bond angles of C1–N1–N2, C2–C3–N3, and N2–N3–C3, 121.9(2)°, 120.5(2)°, and 117.1(2)°, respectively, are relatively small. Similar corresponding values are also observed in 4-Cl, 3-NO_2 lamotrigine $MeSO_3H$ complex [15]. Interestingly, in lamotrigine isethionate, except the C–C–N bond angle (124.2(2)°), all other angles are matching well with the title compound.

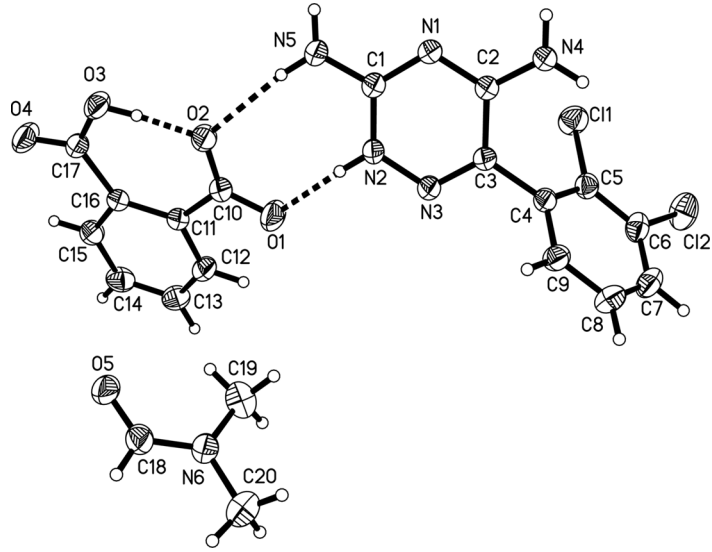

FIGURE 2 View of the title compound, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. The hydrogen bond is shown as a dashed line.

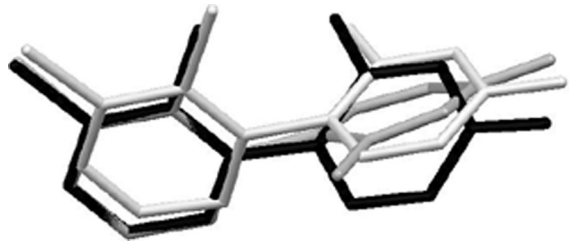

FIGURE 3 Superposition of the title compound (black) with lamotriginium benzoate dimethylformamide (light grey; rms deviation = 0.031 Å) and lamotrigine isethionate (dark grey; rms deviation = 0.016 Å) revealing the tilt in the triazine ring.

In the present structure, the expected proton transfer occurs at N2 of the triazine ring. However, this positive charge associated with the protonation does not alter the triazine ring geometry.

The lamotriginium cations and phthalate anions are linked by an intramolecular N-H...O hydrogen bond forming dimers of an $R^2_2(8)$ type motif [16]. The carbonyl oxygen atom of dimethylformamide solvent as a bridging unit links the lamotriginium cations via intermolecular N-H...O hydrogen bonds, leading to the formation of an inversion related $R_4^2(8)$-type motif (Fig. 4).

Both the intra- (O-H...O and N-H...O) and intermolecular (N-H...O) hydrogen bonds interconnecting the lamotriginium cation and phthalate anion generate a characteristic inversion related $R_6^4(16)$-type motif. Intramolecular O-H...O hydrogen bond interlinks

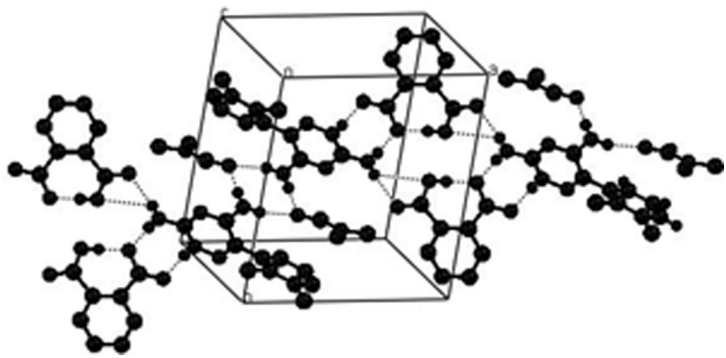

FIGURE 4 Packing diagram of the title compound viewed down the c axis. Dashed lines indicate O-H...O and N-H...O hydrogen bonds. H atoms not involved in hydrogen bonding have been removed for clarity.

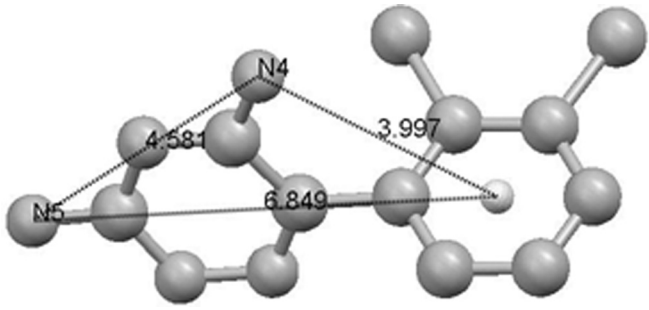

FIGURE 5 Pharmacophore model.

phthalate ion–phthalate ion and leads to the formation of S(7)-type motif. It is noteworthy to mention that the Cl atoms present in the structure are not involved in any interactions.

In the present structure, there is no lamotriginium–lamotriginium cation interaction due to the absence of N-H. . .N hydrogen bonding. However, in the crystal structures of lamotriginium benzoate dimethylformamide solvate and lamotrigine isethionate, N-H. . .N hydrogen bonding is observed that connects the lamotriginium–lamotriginium cation.

According to the pharmacophore model proposed using the five well-known and structurally different compounds, carbamazepine, phenytoin, lamotrigine, zonisamide, and rufinamide, for anticonvulsant activity by Unverferth *et al.* [17], the distance between the first (N4) and the second donor atom (N5) is found to be 3.9–5.5Å, whereas, the distance between the centroid of the aryl ring (marked by grey dot) and the two donor atoms are 3.2–5.1 Å and 4.2–8.5 Å respectively. The corresponding values for the present structure are observed as 3.997 Å, 4.581 Å, and 6.849 Å respectively (Fig. 5).

ACKNOWLEDGMENT

The authors thank J. S. Yadav, director of IICT, for his kind encouragement and support.

REFERENCES

[1] Brodie, M. J. (1992). *Lancet*, *339*, 1397.
[2] Salzjimenez, C. (1994). *Environ. Sci. Technol.*, *28*, 197.
[3] Sridhar, B., & Ravikumar, K. (2005). *Acta Cryst*. *E61*, 3805.

[4] SMART & SAINT (Software reference manuals, versions 6.28a and 5.625). Bruker Analytical X-ray Systems Inc.: Madison, WI. (2001).
[5] Sheldrick, G. M. (1997). *SHELXS97 and SHELXL97, Programs for Crystal Structure Solution and Refinement*. university of Gottingen: Germany.
[6] Sheldrick, G. M. (1990). *SHELXTL/PC user manual*. Bruker Analytical X-ray Systems Inc.: Madison, WI.
[7] Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G., & Taylor, R. (1987). *J. Chem. Soc., Perkin Trans. 2*, S1–19.
[8] Potter, B., Palmer, R. A., Withnall, R., Leach, M. J. & Chowdhry, B. Z. (1999). *J. Chem. Crystallogr.*, *29*(6), 701.
[9] Janes, R. W. & Palmer, R. A. (1995). *Acta Cryst.*, *C51*, 440.
[10] Janes, R. W. & Palmer, R. A. (1995). *Acta Cryst.*, *C51*, 685.
[11] Janes, R. W. & Palmer, R. A. (1996). *Acta Cryst.*, *C52*, 2627.
[12] Janes, R. W. (1999). *J. Chem. Crystallogr.*, *29*(2), 163.
[13] Janes, R. W. (1989). *Acta Crys.*, *C56*, 362.
[14] Atwood, J. L., Krass, D. K., & Paudler, W. W. (1974). *J. Heterocycl. Chem.*, *11*, 743.
[15] Janes, R. W. Ph.D. Thesis, University of London (1992).
[16] Bernstein, J., Davis, R. E., Shimoni, L., & Chang, N. L. (1995). *Angew. Chem. Int. Ed. Engl.*, *34*, 1555.
[17] Unverferth, K., Engel, J., Hofgen, N., Rostock, A., Gunther, R., Lankau, H. J., Menzer, M., Rolfs, A., Liebscher, J., Muller, B., & Hofmann, H. J. (1998). *J. Med. Chem.*, *41*, 63.